REMARKS

Claims 1-66 are pending in this application. Claims 1-11 and 56-66 have been examined and claims 12-55 have been withdrawn from consideration as being drawn to nonelected subject matter. Claims 1, 2, 5-7 were rejected under 35 U.S.C. §102(b). Claims 1-11 and 56-66 were variously rejected under 35 U.S.C. §112, first paragraph.

Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejection under 35 U.S.C. §102(b)

Claims 1, 2, 5-7 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Uhlen, U.S. Pat. No. 5,629,158. Applicants respectfully traverse this rejection.

For a claim to be anticipated by a reference, the reference much teach each and every element of the claim. M.P.E.P. §2131.

As discussed in the response to the Office Action submitted on February 10, 2004, Uhlen describes methods and kits for solid phase diagnosis of medical conditions with procedures performed and complexes used *in vitro*. Uhlen does not teach the use of the complexes in pharmaceutical compositions as claimed.

The Examiner states that this "rejection is drawn to the composition as it pertains to in vitro use, and not as drawn to the intended in vivo use of the composition." However, Applicants respectfully point out that the claimed invention is directed to a pharmaceutical composition comprising IMP/MC complexes and a pharmaceutically acceptable carrier. All elements of the

claimed composition, including the "pharmaceutically accepted carrier," must be included in the examination.

Uhlen is silent with regard to pharmaceutical compositions and pharmaceutically acceptable carriers. Thus, Applicants respectfully submit that the Uhlen does not anticipate the claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b).

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-11 and 56-66 were variously rejected under 35 U.S.C. §112, first paragraph. for allegedly failing to comply with the written description and enablement requirements.

Written Description

Claims 1-11 and 56-66 were rejected as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

The written description requirement "may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure" and compliance with the requirement "is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" See *Amgen, Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.*, USPQ 65 USPQ2d 1385 (Fed. Cir. 2003); *Enzo Biochem, Inc. v Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002). A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi* 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971); MPEP §2163.04.

The claimed invention is directed to a pharmaceutical composition comprising complexes which comprise an immunomodulatory polynucleotide (IMP) linked to the surface of a nonbiodegradable microcarrier.

The Examiner states that the specification "lists various solid phase carriers...as well as listing oil or lipid based microcarriers" and "teaches such pharmaceutical compositions to specifically encompass non-encapsulating (e.g. linked) microparticles." The Examiner asserts, however, that "[n]o description is provided for common structural attributes identifying the members of the genus comprising non-encapsulated (e.g. as opposed to encapsulated) polynucleotide-microcarriers that comprise liposomes, complexes of cholesterol and phospholipid or oil in water in oil emulsions." The Examiner also asserts that "adequate description [has not] been provided for polynucleotide complexes with solid phase microcarriers for administration to an individual or as a component of a pharmaceutical composition." Office Action, page 4. Applicants respectfully disagree with these assertions.

More than merely provided in a list, nonbiodegradable microcarriers (MC) for use in the invention are described throughout the specification, including liquid phase microcarriers. The specification also provides a variety of means and methods for linking an IMP to the surface of an MC. See specification, for example, pages 28, 29, 37-44, 59 and 60. Moreover, Applicants respectfully submit that such microcarriers and methods for linking polynucleotides to the surface of such microcarriers were also very well known in the art at the time the application was filed, as many of the references submitted to the Office on October 24, 2001 with the Information Disclosure Statement demonstrate. In addition, references submitted herewith show that methods for preparation of encapsulated versus non-encapsulated drug with liquid phase microcarriers were known in the art. For example, Li et al. (1993, *Biochem. Biophys. Acta* 1166:145-153) discusses the partitioning of a drug in a liquid phase microcarrier (e.g., a lipid emulsion) between the core and the surface and demonstrates how the partitioning can be shifted to favor surface-attached drug.

Busquets et al. (2003, *Current Drug Targets* 4:633-642) provides a review of methodologies by which materials are associated with liposomes, including how materials can be associated with the outer surface of liposomes. Fix et al (2002, *FEBS Letters* 516:109-112) describes how to deliver drugs to the surface of liquid phase microcarriers.

With regard to the specific assertions regarding liposomes and oil in water emulsions, the specification provides an example, as well as describes a variety of methods known in the art, for the preparation of liquid phase MC with a polynucleotide (IMP) linked to the surface. See, for example, specification pages 39, 40, 43 and 59 (Example 1). In this regard, the specification states "[w]hen the microcarrier is a liposome or other liquid phase microcarrier comprising a lumen, the IMP/MC complex is formed by mixing the IMP and the MC after preparation of the MC, in order to avoid encapsulation of the IMP during the MC preparation process."[1] In addition, methods are known in the art by which linkage of a molecule the surface of a MC as opposed to encapsulation of a molecule within a MC can be tested. See, for example, the fluorescence quenching methods described in the Li et al. (1993) and Fix et al. (2002) references cited herein.

With regard to the alleged lack of description for a pharmaceutical composition, Applicants respectfully submit that the specification describes well known pharmaceutically acceptable carriers and excipients for use in the claimed compositions. The specification also provides a description of a variety of formulations for the IMP/MC complexes appropriate for particular routes of administration. See, for example, specification pages 51, 52, 54 and 59. Moreover, carriers and excipients for formulating pharmaceutical compositions were also very well known in the art at the time the application was filed.

Thus, the specification in combination with that known in the art adequately describes possession of the claimed compositions to one skilled in the art.

---

[1] Specification page 39, line 27, to page 40, line 2.

Applicants respectfully submit that the Examiner has not met the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in the instant disclosure a description of the invention defined in the claims. Thus, a *prima facie* case for lack of written description has not been established.

The pending claims are fully described in the specification as filed. Accordingly, Applicants respectfully submit that the written description requirement has been met.

Enablement

Claims 1-11 and 56-66 were rejected for allegedly not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. Applicants respectfully traverse this rejection.

The court in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), found that the enablement requirement was satisfied by a "disclosure [that] provides considerable direction and guidance on how to practice [the] invention and presents working examples," in view of the fact that "[t]here was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." *Id.* at 740. "Since one embodiment is ... disclosed in the specification, along with the general manner in which its current range was ascertained, ... other permutations of the invention could be practiced by those skilled in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d. 788, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).

In order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); M.P.E.P. §2164.04.

The Examiner states that the specification is "enabling for the in vitro immunomodulation of mouse splenocytes and human PMN cells using the particularly described IMP/MC complexes of examples 1-4." The Examiner also states that the specification "does not

reasonably provide enablement for non-encapsulated microcarriers linked to polynucleotides for administration for treatment to an individual or as a component of a pharmaceutical composition." Office Action, page 5. The Examiner then concludes that "it would require undue experimentation to practice the invention over the scope claimed." Office Action, page 8.

As noted above, the claimed invention is directed to a pharmaceutical composition comprising complexes which comprise an immunomodulatory polynucleotide (IMP) linked to a nonbiodegradable microcarrier. The claimed invention is also directed to kits comprising such complexes.

Although the specification was deemed enabling for *in vitro* compositions, the Examiner states that the specification "fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo administration of the compositions claimed."

Applicants respectfully submit that activity of immunostimulatory polynucleotides *in vivo* is well known in the art. Demonstrating immunostimulatory activity of a ISS-containing polynucleotides in murine splenocytes and human PBMCs in culture are well-known models which correlate with *in vivo* immunostimulatory activity of the polynucleotides. See, for example, the following references of record: WO 99/11275 (related to U.S. Pat. No. 6,498,148), WO 98/16247 (related to U.S. Pat. No. 6,610,661) and WO 98/55495 (related to U.S. Pat. No. 6,589,940).

If the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995); M.P.E.P. §2164.02. The Examiner has not provided evidence to support or reasons for a conclusion of lack of correlation for the *in vitro* model examples and *in vivo* activity for the claimed compositions.

In support of the rejection, the Examiner cites the Gold, Kasid and Collins references[2] as indicating that the art is silent with regard to "the treatment effects of pharmaceutical compositions comprising non-encapsulated IMP/MC complexes in a subject." Office Action, page 6. All three references discuss encapsulation of polynucleotides within liposomes. However, none of the references discuss pharmaceutical compositions comprising complexes of a polynucleotide linked to the surface of a liposome or any nonbiodegradable microcarrier. Applicants respectfully submit that citing three cited references which are silent with regard to the claimed subject matter does not support the alleged state of unpredictability with regard to the claimed invention and thus, does not provide acceptable documentation to support any doubt of the teachings of the specification. Nor do these references provide any evidence to support a conclusion of lack of correlation for the *in vitro* model examples and *in vivo* activity for the claimed compositions Thus, these references do not support that the claimed invention is not enabled.

The Examiner asserts that the specification has not provided guidance "toward a method of generating non-encapsulated IMP/MC, whereby the microcarrier is liquid phase" or toward a "method of producing non-encapsulated IMP/MC compositions for administration in a subject or as a component for a pharmaceutical composition." Office Action, pages 6-7. Applicants respectfully disagree with this assertion for the reasons discussed herein regarding specification support for this subject matter in the section addressing the written description rejection.

Accordingly, Applicants respectfully submit that the Examiner has not provided acceptable documentation or sound scientific reasoning to support any doubt of the teachings of the specification. See, for example, *In re Marzocchi*, 439 F2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). Unless such documentation and/or scientific reasoning are adduced, the statements made in the specification are to be taken at face value.

[2] Gold et al. (U.S. Pat. No. 6,465,188, "Gold"), Kasid et al. (U.S. Pat. No. 6,559,129, "Kasid") and Collins (U.S. Pat. No. 6,355,267), all cited in Office Action.

Thus, Applicants respectfully submit that a *prima facie* case of lack of enablement has not been established. Accordingly, the pending claims are in compliance with the enablement requirements.

In sum, Applicants submit that the pending claims fall within the subject matter that is described and enabled by the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 377882001700. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: September 20, 2004

Respectfully submitted,

By _____

Karen Zachow, Ph.D.
Registration No.: 46,332
MORRISON & FOERSTER LLP
3811 Valley Centre Drive, Suite 500
San Diego, California 92130
(858) 720-5191